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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/881,475	SNODGRASS, H. RALPH
	Examiner	Art Unit
	Daniel M Sullivan	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20 and 34-56* is/are pending in the application.

4a) Of the above claim(s) *19,20 and 34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-18 and 42-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
4)☐ Interview Summary (PTO-413) Paper No(s). ____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

This Non-Final Office Action is a reply to the "Amendment under 37 CFR §1.111" of 6 August 2003 (hereinafter, 6 August Paper), filed in response to the Non-Final Office Action mailed 6 February 2003 (hereinafter, 6 February Office Action). Claims 19, 20 and 34-41 were withdrawn from consideration and claims 1-18 and 21-33 were considered in the 6 February Office Action. Claims 1 and 21-33 were canceled, claims 2, 3, 5, 7, 11-13 and 16-18 were amended and claims 42-56 were added in the 6 August Paper. Claims 2-20 and 34-56 are pending, and claims 2-18 and 42-56 are under consideration.

Claims 19, 20 and 34-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 22 November 2002.

Election/Restrictions

Newly submitted claim 46 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The subject matter of claim 46, directed to a method for prioritizing drug development, is distinct from the subject matter of elected Invention I, directed to a method of creating a molecular profile of a chemical composition. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the inventions are not disclosed as capable of use together. None of the originally filed claims are

directed to a method of prioritizing drug development, the originally filed specification makes no reference to a method of prioritizing drug development and there are no method steps set forth in the original disclosure to adapt the method of ranking or typing toxicity to a method for prioritizing drug development. Thus, the originally filed disclosure does not even contemplate a method for prioritizing drug development, let alone disclose how the method can be used together with a method of creating a molecular profile. Furthermore, the method of prioritizing drug development has a different mode of operation and effect because the term suggests that the method comprises a decision tree, which is used to develop a business strategy.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 46 is withdrawn from consideration as being directed to a non-elected invention. Furthermore, claims 47-56 will be examined only insofar as they depend from claims 42-45. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Amendment

Rejection of claims 1 and 21-33 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 112

Rejection of claims 2-18 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claim 5 under 35 U.S.C. 102(a) as anticipated by Ji *et al.* (2000) *J. Bone Mineral Metab.* 18:132-139 is withdrawn.

Rejection of claims 2, 7 and 10 under 35 U.S.C. 102(b) as anticipated by Church *et al.* (May 1999) *Calc. Tissue Int.* 64:S54 is withdrawn.

Rejection of claims 2-4, 7, 8 and 10 under 35 U.S.C. 102(a) as being anticipated by Bruder *et al.* (1998) U.S. Patent No. 5,736,396 is withdrawn.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-18 and 42-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not

limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant invention is directed to a method of compiling a library of molecular profiles of chemical compositions and a method of typing, ranking or assessing toxicity of a test chemical composition comprising contacting an isolated population of mammalian mesenchymal stem cells (MSC) with said chemical compositions. The chemical compositions of the claims are not limited to any particular type of composition, or in dependent claims limited to therapeutic agents, neurotoxins renal toxins hepatic toxins, toxins of hematopoietic cells, myotoxins, agents toxic to reproductive organs, teratogenic agents, carcinogens, agricultural chemicals, cosmetics and environmental contaminants. The specification teaches that the claimed methods can be used to assess toxicity of chemical compositions by comparing expression patterns of MSC's exposed to new or previously untested agents to a library of profiles of expression induced by agents of known toxicity, such that predictions can be made as to the likely type of toxicity of the new agent (page 14, first full paragraph). The specification asserts, "the outcome of such comparisons provides information for one to predict the likelihood of whether the test composition is toxic, what type of toxicities, and how toxic it would be as compared to other compositions" (final paragraph on page 34). It is also clear from teachings found throughout the specification that the invention is intended to be used to predict the toxic effects that would be manifest *in vivo*. As the enabling

disclosure must teach the skilled artisan how to make the claimed invention such that it can be used for the purposes contemplated therein, the specification must teach the skilled artisan how to make a library of molecular profiles of chemical compositions that can be used to predict the likelihood of whether a test composition is toxic, what type of toxicity, and how toxic it would be as compared to other compositions; and how to type, rank and assess toxicity of a test chemical composition using data obtained by contacting an isolated population of mammalian MSCs with the test chemical composition and comparing the molecular profile of the test chemical composition with a library of molecular profiles.

State of the prior art and level of predictability in the art: The relevant art teaches that establishing an *in vitro* model system having the capacity to predict the likelihood of toxicity, the type of toxicity, and/or the degree of toxicity is far from routine.

First, the art teaches that, before an *in vitro* system can be used to predict the *in vivo* toxicity of a compound, the model system must be validated. Davila *et al.* (1998) *Annu. Rev. Toxicol.* 38:63-96, teaches that before *in vitro* findings may be correlated with *in vivo* human toxicity, certain basic steps should be followed (page 64). These include: identify the appropriate target organ and species; develop and characterize a suitable *in vitro* system; with model test compounds and reasonable *in vitro* concentrations and exposure times, perform toxicity studies; employ a battery of cytotoxic assays to evaluate the compounds; after evaluation of the model compounds, measure the toxicity of unknown or previously untested agents; compare and contrast their toxicity with the model compounds; and examine mechanisms of toxicity with more detailed and in-depth investigations (Table 1). Davila teaches, "[a]fter thorough examination of the model compounds to demonstrate the validity and sensitivity of the *in vitro*

system to detect known toxic compounds, unknown or untested compounds can be evaluated with the *in vitro* model system" (bridging pages 64-65). Thus, Davila teaches that careful experimentation is required to establish that the endpoint measured in the *in vitro* model system can be reliably correlated with a given *in vivo* toxicity before data obtained *in vitro* can be used to predict the toxic properties of a compound as they are manifest *in vivo*.

In an article published well after the effective filing date of the instant application, Waring *et al.* (2002) *Curr. Opin. Mol. Ther.* 4:229-235 also questions the predictive value of *in vitro* systems, particularly with respect to toxicogenomic methods. Waring *et al.* flatly states, "[i]t is too early to determine if gene expression markers for toxicity can be extrapolated from cell culture to animal systems" and "[c]learly, a great deal of additional research will be required in order to consistently link the changes seen *in vivo* and *in vitro*" (page 233, left column, second full paragraph). These assertions are based, in part, on the observation that 15 well-characterized hepatotoxins grouped together differently and gave very different expression profiles in isolated rat hepatocytes versus in-life-treated rats. Tugwood *et al.* (2003) *Biomarkers* 8:79-92 also questions the predictive value of *in vitro* experiments and particularly emphasizes the dedifferentiation of primary isolates in culture as a confounding factor in correlating *in vitro* data to *in vivo* effects (see especially the first full paragraph on page 84). These findings call into question even the limited expectation that toxicogenomic data obtained with a cells isolated from a particular organ can predict similar effects in that same organ *in vivo*, let alone an expectation that toxicogenomic data obtained *in vitro* using a primitive cell type can be used to generally predict toxicity in the many varied cell types that make up an animal.

Waring *et al.* teaches that among the questions that remain to be addressed even in 2002 are: whether gene expression alone is enough to predict and/or identify a mechanism of toxicity; how great the an effect time points and concentrations will have on the overall expression profile; and the ability of microarray analysis to identify cell-specific toxicity (third full paragraph in the left column on page 233). Furthermore, Waring *et al.* characterizes the majority of toxicogenomics used for safety evaluation as of 2002 as exploratory and applied in a case-by-case fashion. As a whole, the teachings of Waring *et al.* and Tugwood *et al.* indicate that the validity of *in vitro* toxicogenomic models for toxicity is at least as unpredictable as other systems, and also requires careful empirical verification to establish the predictive capabilities of the model system as described by Davila *et al.*

With regard to using primary cultures of MSCs to predict the *in vivo* toxic effects of a wide range of compounds, the art is mostly silent. Carere *et al.* (2002) *Toxicol. Lett.* 127:153-160 speculates that stem cells may provide a source of specialized cell types and may allow the study of toxicant interferences with development and specialization processes (paragraph bridging the left and right columns on page 155), but characterizes the state of the art in 2002 as "not ready for standardization and routine use" (second full paragraph in the right column on page 155).

The art also teaches that the correlative value of any particular toxicogenomic method is also unpredictable. Thomas *et al.* (2003; *Toxicogenomics*, pp. 31-38. Editor(s): Inoue and Pennie. Springer-Verlag Tokyo: Tokyo, Japan) teaches, "just identifying the disrupted pathways and associated gene expression changes do not necessarily provide a method to predict similar toxic responses with other chemicals or across species. A big challenge for the emerging field of toxicogenomics will be to develop models and tools that use gene expression measurements to

ultimately predict toxicity in untested chemicals and also determine whether a similar toxic response will occur in humans" (first paragraph on page 32). Thus, Thomas *et al.* teaches that developing models and tools that use gene expression measurements to ultimately predict toxicity in untested chemicals remained a challenge to be overcome as late as 2003, and therefore was clearly not routine when the instant application was filed.

Thomas *et al.* teaches that there are two important points concerning development of predictive toxicological models using gene expression: the information contained within the predictor variables and the selection of a diagnostic subset of genes (first full paragraph on page 34). Thomas *et al.* teaches, "the classification of a set of chemicals into a toxicological class or endpoint based on gene expression is difficult due to the variety of potential mechanisms that underlie the toxicity of these chemicals" and cites examples of compounds that arrive at the same toxic endpoint by distinct pathways (page 34). Thomas further teaches that interpreting toxicogenomic data is also complicated by the fact that "multiple factors converge to ultimately influence the manifestation of toxicity and associated gene expression patterns" (paragraph bridging pages 34-35). Although Thomas *et al.* is referring to the *in vivo* system, it is reasonable to assume that because factors such as time, dose, route of administration, age and sex would not be accounted for in *in vitro* models, these factors would create even greater uncertainty in using findings obtained in an *in vitro* system to predict the likelihood of whether a test composition is toxic, what type of toxicity, and how toxic it would be as compared to other compositions.

Thus, the teachings from the art clearly establish that at the time of filing, and well after, the skilled artisan would not be able to predict the presence, type or degree of toxicity based on data obtained with an *in vitro* toxicogenomic model without first establishing a nexus between

the model system and the relevant *in vivo* system. Furthermore, the art teaches that establishing the nexus between an *in vitro* toxicogenomic system and an *in vivo* system was far from routine at the time of filing. Therefore, the skilled artisan must rely on the teachings of the instant disclosure to set forth the manner and process of making a library of molecular profiles of chemical compositions that can be used to predict the likelihood of whether a test composition is toxic, what type of toxicity, and how toxic it would be as compared to other compositions; and how to type, rank and assess toxicity of a test chemical composition using data obtained by contacting an isolated population of mammalian MSCs with the test chemical composition and comparing the molecular profile of the test chemical composition with a library of molecular profile. Furthermore, these teachings must be set forth in such clear, concise, and exact terms as to enable the skilled artisan to practice the invention without undue experimentation.

Amount of direction provided by the inventor and existence of working examples: With regard to working examples, the specification describes a process of making a library of molecular profiles wherein alterations in protein expression elicited in MSCs by two different test compositions are determined (see especially Figures 1-4 and the legends thereto). However, the specification is silent with regard to the predictive value of the data set presented and provides no evidence that the data can be used to establish the toxic properties of a test compound. Thus, the specification does not appear to contain a single working example of the invention. Therefore, the question at hand is whether the specification provides sufficient teaching to enable the skilled artisan to extend the method reduced to practice such that it could be used for the purpose set forth in the specification without the need for undue experimentation.

On page 10, the specification asserts that the invention achieves the goals set forth in the specification by "exploiting the properties of pluripotent mesenchymal stem cells (MSC's)." Applicant speculates that, "[b]ecause of its pluripotency in differentiating into multiple tissue types, an isolated population of MSCs provides a much closer model to the complexity of *in vivo* systems than do traditional single cell or yeast assays" (paragraph bridging pages 10-11). However, this statement seems to be at odds with the teachings of Tugwood *et al.*, which suggest that dedifferentiation is damaging to the correlative value of an *in vitro* model system. Applicant's assertion seems to be based on a hypothesis that the relatively primitive nature of MSC's makes them more representative of the complex biology of an intact organism (see e.g., the first and second full paragraphs on page 2), yet no data are presented to support this hypothesis. With regard to correlating the molecular profiles with toxicities, the specification merely teaches that repeated iteration of the method of compiling a library of molecular profiles with "a reasonably large number" of chemical compounds of similar toxicity will provide patterns of gene or protein expression, or both, associated with that toxicity. However, this simple scheme for providing correlative data fails to account for the many variables that might confound obtaining a predictive data set, such as cell type specific effects, various pathways leading to common toxic outcomes, bioconversion of some compounds to toxic metabolites and various pharmacodynamic effects present in the *in vivo* system (e.g., sequestration or compartmentalization) that would not be accounted for in the *in vitro* system. Likewise, the teachings from the specification regarding how toxicities can by typed or ranked using the claimed method provide only that the molecular profile of test composition can be compared to that of a chemical composition or library of compositions with predetermined toxicities and the

outcome of the comparison provides information for one to predict the likelihood of whether the test composition is toxic, what type of toxicities, and how toxic it would be as compared to the other known toxic compositions. However, these teachings are predicated on the assumption that expression profiles in MSC's are a viable model for toxicity *in vivo*, and that the system provides an accurate measure of toxicity regardless of the toxicant (i.e., to therapeutic agents, neurotoxins renal toxins hepatic toxins, toxins of hematopoietic cells, myotoxins, agents toxic to reproductive organs, teratogenic agents, carcinogens, agricultural chemicals, cosmetics and environmental contaminants) or organ system affected by the toxicity. Again, however, no data are provided to support this assumption. Thus, the specification stops well short of teaching the skilled artisan how the data obtained according to the claimed method relate to the toxic properties of the test compounds as they are manifest *in vivo*.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Given the art recognized unpredictability of extrapolating *in vitro* toxicogenomic data to predict *in vivo* toxicity for any given type of toxicity or target organ, the skilled artisan would clearly have to engage in undue empirical experimentation to confirm that the claimed method could be used to predict any particular type of toxicity in any particular organ system, let alone the broad scope contemplated in the application. Davila *et al.* teaches that merely establishing that the claimed method could be used to predict a single type of toxicity to a single organ system would require developing and characterizing the *in vitro* MSC system as a model for the appropriate target organs; performing toxicity studies with model test compounds at reasonable *in vitro* concentrations and exposure times; employing a battery of cytotoxic assays to evaluate the compounds; after evaluation of the model compounds, measuring the toxicity of

unknown or previously untested agents; comparing and contrasting their toxicity with the model compounds; and examining mechanisms of toxicity with more detailed and in-depth investigations.

The art published even well after the effective filing date of the in instant application teaches that "it is too early to determine if gene expression markers for toxicity can be extrapolated from cell culture to animal systems" and "[c]learly, a great deal of additional research will be required in order to consistently link the changes seen *in vivo* and *in vitro*" (*Id.*), and identifies developing models and tools that use gene expression measurements to ultimately predict toxicity in untested chemicals and also determine whether a similar toxic response will occur in human as a big challenge for the emerging field of toxicogenomics (*Id.*). Clearly, therefore, the task of developing the instant claimed method such that it can be used to predict the likelihood of whether the test composition is toxic, what type of toxicities, and how toxic it would be as compared to the other known toxic compositions would require experimentation well beyond what is considered routine in the art. Therefore, claims 2-18 and 42-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER